Biopesticides and

Pollution Prevention Division

Office of Pesticide Programs

Microbial Pesticide Regulation

US Environmental Protection Agency
Office of Pesticide Programs
Biopesticides & Pollution Prevention Division

www.epa.gov/pesticides/biopesticides

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Microbial Pesticide Regulation

- Microbial Pesticide:
  - Microbial agent intended for preventing, destroying, repelling, or mitigating any pest, or intended for use as a plant regulator, defoliant, or desiccant.
- Starts at 40 CFR 158.2100.
  - Live or Dead microbes.
    - Eukaryote.
    - Prokaryote.
    - Parasitically replicating microscopic element.
      - DNA / RNA / Protein = Dead microbe, biochemical or conventional?
      - Other BioControl Agents, e.g. beneficial insects and nematodes, have been exempted from regulation as pesticides.
        - » Unless microbial symbiont is changed (paratransgenesis).
  - Registration and EUP requirements.
    - No EUP needed if <10 acres land, <1 acre water, and crop destruct.
    - Biotech derived pesticides need a notification for an environmental release.
    - EUP purpose is to develop data for a registration.

Microbial Pesticide Regulation

- Data Requirements and Guidelines – Tier I.
  - Product Characterization: 40 CFR 158.2120
    - Biological and Chemical properties.
    - Manufacture.
    - Label and CSF.
  - Health Effects: 40 CFR 158.2140
    - Infectivity / toxicity / pathogenicity testing.
      - Clearance from organs and tissues.
      - Check for subchronic/chronic infection.
    - Toxicity testing.
    - Irritation testing.
  - Nontarget Effects: 40 CFR 158.2150
    - Avian, wild mammal, fish, aquatic invertebrates, plants, insects, Honeybees.
  - Food Tolerance Exemption Petition.

Microbial Pesticide Regulation

- Data Requirements and Guidelines Tier II-IV.
  - Product Characterization:
    - Microbe is in NIH Risk Group / Biosafety Level 2-4.
    - Metabolite or microbe is a Select Agent.
    - Known agent of foodborne illness.
  - Health Effects:
    - Infects non-inoculated tissues or does not clear.
    - Pathogenicity.
    - Produces an unexpected toxin or toxic metabolite.
  - Nontarget Effects: 40 CFR 158.2150
    - Metabolite or microbe is a Select Agent.
    - Nonspecific Plant or Animal pathogen.
    - Nonspecific toxin or metabolite produced.
  - Tier II-IV requires Residue data: 40 CFR 158.2130.

Microbial Pesticide Regulation

Product Analysis

Human Health Tier I

Tox/Pathology & tox studies

Non-Target Organism Tier I

Acute organism testing

If significant effects are seen in Tier I

If significant toxicity or persistance is seen in Tier I
Also for toxic metabolites

Non-Target Organism Tier II

Environmental expression

Human Health Tier II

Acute & subchronic tox

If significant effects are seen in Tier I
& Tier II indicates exposure

If significant toxicity seen at Tier II or to assess suspected human pahogens or viruses

Non-Target Organism Tier III

Mesocosm testing

Human Health Tier III

Additional Toxicity testing and/or Toxicity/infectivity analysis

If lower Tier results suggest unreasonable environment effects. May be conducted as a condition of registration if risks appear to be acceptable.

Non-Target Organism Tier IV

Simulated or Actual Field tests

Toxicity/Pathogenicity Testing

- Health Effects:
  - Maximum hazard dose testing:
    - 10^8 units via oral & pulmonary routes.
    - 10^7 units if injected:
      - i.v. bacteria, viruses.
      - i.p. fungi, protozoa.
  - 3 animals/sex at each interim & final sacrifice.
  - Continue until a pattern of clearance is seen.
- Nontarget Organisms:
  - Avian oral: [MPCA] in TGAI x 5 mL/kg BW x weight of test bird (kg).
  - Avian inhalation: [MPCA] in TGAI x 0.2 mL/kg BW x weight of test bird (kg).
  - Fish / Invertebrates: At least10^6 units/mL in water 'or' 1,000x the maximum concentration in 6" water and 100x in feed (whichever is greater and attainable).
  - Plants: Maximum label use rate.
  - Insects: Increments to 100x the LD_{50} or LC_{50} 'or' 10-100x maximum label use rate.
  - Honeybees: Consult an EPA entomologist – could be whole hive, larval etc.

Toxicity/Pathogenicity Testing

- Clinical observation / examination of animals.
  - Morbidity and mortality
- Body weight gain.
- Necropsy – compared with controls.
  - Gross pathology.
  - Organ weights.
- Enumeration of microbial active ingredient.
  - To determine infectivity.
  - To show pattern of clearance.
  - Kidney, brain, liver, lung, stomach, intestines, cecum, spleen, blood, etc.

Microbial Pesticide Registration

- Genetically modified microbes:
  - Same as for natural isolates, except:
  - **OCSPP Guideline No. 885.1100:** "If the MPCA in question has been altered genetically ….. the methods used to alter the microbe genetically should be provided. In the case of genetically altered products, the identity of the inserted or deleted genetic material (source, nature, size, base sequence data and/or restriction endonuclease map), information on the gene control region, descriptions of the phenotypic traits to be gained or lost, and information as to the genetic stability (reversion tendency or rate of exchange/transfer with other organisms) of the genetically altered chromosomal region or extrachromosomal entity are to be discussed. Genetic material adjacent to the intentionally inserted genes which may have been engineered into the recipient are to be fully characterized and the likelihood of expression must be provided."
  - Experimental Uses: 40 CFR 172.45
    - **Biotech notification process** determines if an EUP or registration is needed for field tests.

Summary: Regulatory Process

- FIFRA as amended by FQPA:
  - Will unreasonable effects (to man or the environment) result from uses as labeled?
  - Is there a ‘may affect’ endangered species finding?
- FFDCA:
  - Is an exemption from the requirement of a food tolerance supportable?
  - Is a numerical tolerance, with generation of residue data, necessary or warranted?
- Label and CSF:
  - Should have matching data.
  - Contain risk mitigation information (PPE, REI, etc.).
- **Data waivers:**
  - Data and/or literature that closely address study endpoints.

Risk Assessment

- Hazard:
  - Toxicity, Infectivity, Pathogenicity.
- Exposure:
  - Label: Scale of use, use patterns, application rates.
  - Persistence, degradation, mobility.
    - Water (i.e. irrigation, drinking and recreational use).
    - Soil.
    - Plant materials.
  - Population dynamics, residues.
    - Difficult analysis for microbials that multiply in the environment .
    - Microbial toxins and metabolites may need analysis.
- Risk:
  - Non-target organisms, humans including susceptible populations, domestic animals, endangered species.

Microbial Pesticides

Regulatory Challenges

- Killed microbes
  - Case-by-case to assure sufficiently killed.
  - May require conventional analysis of the toxins.
- Microbial mixtures
  - Need to identify each active as a separate a.i., but may test the consortium for guideline studies.
- Animal and plant pathogens
  - Our guidelines are designed to weed these out.
- Biotech products
  - DNA / RNA and metabolites may not fit the microbial definition (but they are pesticides).
  - Our guidelines are designed for microbes.

Microbial Pesticides
Usually Done Right

- Pre-registration meeting.
- Follows relevant Pesticide Registration (PR) notices and 40 CFR.
- Data matrix – relevant studies addressed.
- Copies of cited literature are submitted.
- Contact / Agent is responsive if minutiae need to be addressed during review.

Microbial Pesticides
Often Not Done Right

- Data requirements are only not required (NR) if meeting notes are signed by our DD.
- The latest taxonomy is not addressed.
  - Spend time on OCSPP 885.1100.
- The mode of action and/or metabolites are listed as ‘unknown’.
- Endangered species are not considered.
- Viability or activity units are missing.
- Tox. rather than tox./path. tests done.
- Data waivers do not qualify for Tox. Cat. IV.

Microbial Pesticides

Data Needs

- Appropriate Non-target tests:
  - Aquatic insects / invertebrates.
- Appropriate tests for:
  - DNA / RNA.
  - Proteins.
    - Are bioinformatics enough?
- Should we focus on joints reviews?
  - NAFTA.
  - OECD.
  - What data format is best – how about electronic?